A study comparing intermittent with continuous treatment with BTK inhibitors in chronic lymphocytic leukaemia (CLL)

Submission date	Recruitment status Recruiting	[X] Prospectively registered		
21/06/2022		☐ Protocol		
Registration date	Overall study status	Statistical analysis plan		
27/06/2022	Ongoing Condition category	☐ Results		
Last Edited		Individual participant data		
25/09/2025	Cancer	[X] Record updated in last year		

Plain English summary of protocol

Background and study aims

Ibrutinib and acalabrutinib are part of a group of drugs for chronic lymphocytic leukaemia (CLL) called targeted drugs. Targeted drugs have fewer side effects than traditional chemotherapy. However, as the drug is usually taken for several years, these side effects can be a burden.

There is some evidence that, if ibrutinib or acalabrutinib is taken for several years, the CLL is more likely to become resistant to this treatment. STATIC will investigated whether having a break from treatment will work as well as continuing treatment without a break, if whether taking a break from treatment reduces side effects, whether it lowers the risk of CLL becoming resistant to ibrutinib or acalabrutinib, and whether there is any difference in the overall cost of CLL treatment. We also want to know whether having a break from treatment changes how patients are feeling emotionally.

Who can participate?

830 patients will be enrolled into the STATIC trial. These patients will be made up of patients who have been treated on the NHS with ibrutinib or acalabrutinib as their second or subsequent treatment for their CLL as well as those who have been treated in other studies called the FLAIR and IcICLLe trials, and those who have been treated with ibrutinib in standard care as their first line of treatment.

What does the study involve?

Patients in the randomisation trial will be randomly allocated to have either continuous or intermittent treatment with the same BTK inhibitor they have already been treated with. A small number of patients finishing FLAIR will be advised to continue ibrutinib as their CLL is not well controlled enough for them to take part in the randomised trial and they can continue ibrutinib treatment in STATIC without being randomised.

What are the possible benefits and risks of participating?

We hope that participants will be helped by taking part in this study, but we can't guarantee this. However, the information we get from this study will contribute to medical research and help us

improve future treatments for people who have CLL. As we learn more about the effects of taking ibrutinib and acalabrutinib for longer periods of time, pausing treatment for periods, and how this changes the side effects, this may lead to future changes in treatment for CLL patients. The STATIC Randomised trial will help to understand whether pausing treatment when CLL is well controlled is as good as continuing treatment without a break. Both the randomised trial and clinical need group will give us information about the effects of taking ibrutinib and acalabrutinib for a long time as well as the benefits and safety of ibrutinib and acalabrutinib. Both participants who are randomised to continuous treatment and who enter the patient need cohort will receive treatment for longer periods than standard care, which may prolong the presence of side effects. Participants will be closely monitored and will attend regular outpatient appointments to monitor this, and the side effects can often be managed by lowering drug dose or taking supportive medication.

Participants randomised to the intermittent treatment may have concerns about pausing treatment. However, treatment will only be paused in the trial when a patient is in a good remission, which may last for some considerable time, and will resume treatment when there are early signs of CLL reappearing.

Where is the study run from? University of Leeds (UK)

When is the study starting and how long is it expected to run for? June 2022 to September 2031

Who is funding the study? National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (UK) Janssen-Cliag (UK)

Who is the main contact? Doina Levinte static@leeds.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-ibrutinib-with-and-without-treatment-breaks-for-chronic-lymphocytic-leukaemia-static

Contact information

Type(s)

Scientific

Contact name

Ms Doina Levinte

Contact details

Clinical Trials Research Unit Leeds Institute of Clinical Trials Research University of Leeds Leeds United Kingdom

Additional identifiers

Clinical Trials Information System (CTIS)

2021-005854-27

Integrated Research Application System (IRAS)

1003615

ClinicalTrials.gov (NCT)

Nil known

Protocol serial number

HM21/142069, IRAS 1003615, CPMS 52879

Study information

Scientific Title

A randomised phase III trial comparing intermittent with continuous treatment strategies in chronic lymphocytic leukaemia (CLL)

Acronym

STATIC

Study objectives

Current study objectives as of 07/07/2025:

An intermittent treatment strategy using a BTK inhibitor (including ibrutinib or acalabrutinib) will reduce treatment-emergent resistance and thus be at least non-inferior to continuous treatment with regards to time to treatment strategy failure whilst reducing resource impact for the NHS and improving quality of life.

Previous study objectives:

An intermittent treatment strategy using ibrutinib, will reduce treatment-emergent resistance and thus be at least non-inferior to continuous treatment with regards to time to treatment strategy failure whilst reducing resource impact for the NHS and improving quality of life.

Ethics approval required

Old ethics approval format

Ethics approval(s)

- 1. Approved 10/08/2022, HRA and Health and Care Research Wales (HCRW) (Health Research Authority, 2 Redman Place, London, E20 1JQ, United Kingdom; Tel: N/A; approvals@hra.nhs.uk), ref: 1003615
- 2. Approved 03/08/2022, MHRA (10 South Colonnade, Canary Wharf, London, E14 4PU, United Kingdom; +44 (0)20 3080 6000; info@mhra.gov.uk), ref: 1003615
- 3. Approved 02/08/2022, Health Research Authority (REC), North East York Research Ethics Committee (North East York Research Ethics Committee, NHSBT Newcastle Blood Donor

Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; +44 (0)207 104 8079; york.rec@hra.nhs.uk), ref: 1003615

Study design

STATIC is designed with multiple pathways, the 'Randomization Pathway' and the 'Clinical Need Cohort', which route a participant enters will be determined by their eligibility.

Randomisation Trial: A prospective, national, multicentre, open-label, randomized, controlled, two-arm, parallel-group, non-inferiority, Phase III trial to assess whether patients with CLL on long-term treatment with a BTK inhibitor (including ibrutinib or acalabrutinib) have similar disease control with an intermittent treatment strategy (experimental arm) compared with standard continuous treatment (control arm).

Clinical Need Cohort: A prospective, national, multicentre, open-label, single-arm, non-randomized cohort to assess the safety and overall survival of patients with CLL receiving long-term continuous treatment with ibrutinib.

Primary study design

Interventional

Study type(s)

Treatment

Health condition(s) or problem(s) studied

Chronic lymphocytic leukaemia (CLL)

Interventions

Current interventions as of 07/07/2025:

In the randomisation pathway, participants will be randomised 1:1 to either intermittent treatment with a BTK inhibitor, known as the 'pausing treatment' arm, or continuous treatment. Participants randomised to continuous treatment will receive either ibrutinib (oral) 420 mg per day (or other reduced dose, if that dose has been stable for the past 6 months and there are no unresolved toxicities) or acalabrutinib (oral) 200 mg per day (or other reduced dose, if that dose has been stable for the past 6 months and there are no unresolved toxicities), until strategy failure, defined as active disease as per 2018 iwCLL criteria, death, or the end of the trial.

Participants randomised to the 'pausing treatment' arm (intermittent treatment strategy) will pause BTK inhibitor treatment immediately following randomisation, and restart when the restart criteria are met. When treatment restarts, participants restart BTK inhibitor treatment at the standard dose (or their previous stable reduced dose) until the treatment pausing criteria are met. The pausing and resuming criteria are assessed locally every 3 months at standard clinic visits. Participants can pause and restart treatment multiple times until treatment strategy failure (defined as active disease per 2018 iwCLL criteria) whilst on treatment, death, or end of the study.

In the Clinical Need Cohort all participants will receive ibrutinib (continuous treatment), either at the recommended starting dose or the stable reduced dose they were receiving at the end of the FLAIR or IcICLLe trial, but will not be randomised. Participants in the Clinical Need Cohort will receive treatment during the trials 6 6-year recruitment period and for the 3 years of follow-up, meaning that participants will be on the trial for between 3-9 years, depending upon when they enter the trial.

Previous interventions:

In the randomisation pathway participants will be randomised 1:1 to either intermittent ibrutinib, known as the 'pausing ibrutinib' arm, or continuous ibrutinib treatment. Participants randomised to continuous treatment will receive ibrutinib (oral) 420 mg per day (or other reduced dose, if that dose has been stable for the past 6 months and there are no unresolved toxicities) until strategy failure, defined as active disease as per 2018 iwCLL criteria, death, or the end of the trial.

Participants randomised to the 'pausing ibrutinib' arm (intermittent treatment strategy) will pause ibrutinib treatment immediately following randomisation, and restart when the restart criteria are met. When treatment restarts, participants restart ibrutinib treatment at the standard dose (or their previous stable reduced dose) until the treatment pausing criteria are met. The pausing and resuming criteria are assessed locally every 3 months at standard clinic visits. Participants can pause and restart treatment multiple times until treatment strategy failure (defined as active disease per 2018 iwCLL criteria) whilst on treatment, death, or end of the study.

In the Clinical Need Cohort all participants will to receive ibrutinib (continuous treatment), either at the recommended starting dose, or the stable reduced dose they were receiving at the end of the FLAIR trial, but will not be randomised. Participants in the Clinical Need Cohort will receive treatment during the trials 6 year recruitment period and for the 3 years of follow up, meaning that participants will be on the trial for between 3-9 years, depending upon when they enter the trial.

Intervention Type

Drug

Phase

Phase III

Drug/device/biological/vaccine name(s)

Ibrutinib (Imbruvica), acalabrutinib (Calquence)

Primary outcome(s)

Time to treatment strategy failure. Time to treatment strategy failure is defined as the time from randomisation to time of treatment strategy failure. Treatment strategy failure is defined as the first documented instance of active disease that does not respond to treatment, or death from any cause measured using patient records throughout the study

Key secondary outcome(s))

- 1. Overall survival will be measured for the randomisation trial as the time from randomisation to the time of death from any cause. In the clinical need cohort this will be calculated as the time from registration to the time of death from any cause.
- 2. Toxicity and tolerability based on adverse events, as graded by CTCAE V5.0 and determined by routine clinical assessments at each centre.
- 3. Cost-effectiveness is defined as a cost per incremental QALY below £20,000 and/or a positive incremental net monetary benefit. The cost-effectiveness of treatment options will be evaluated with respect to this criteria.
- 4. Quality of life will be assessed using the patient-reported outcome measures: EORTC-QLQ-C30, EORTC-QLQ-CLL and EQ-5D-5L. This will be measured in the randomisation trial only and will be recorded at baseline and after 3, 6 12, 18, 24, 30, 36 and 48 months of trial treatment.

- 5. Summative treatment-free Interval is defined as the time to treatment strategy failure, excluding any time spent on treatment.
- 6. Response to retreatment in intermittent treatment arm will be assessed as a patients response (partial remission (PR), stable disease (SD) or progressive disease (PD) according to the response criteria defined by the standard 2018 iwCLL criteria) between 9 and 12 months after restarting treatment.
- 7. Time to next treatment is defined as the time from randomisation to the start date of the next line of treatment. For the Clinical Need Cohort, this will be time from registration to the start date of the next line of treatment.
- 8. Response to next treatment for CLL will be assessed as the best response (PR, SD or PD according to the response criteria defined by the standard 2018 iwCLL criteria) achieved by a participant at any timepoint.
- 9. Rate of resistance mutation between trial arms will be assessed as the proportion of participants in each arm with a detectable BTK mutation at baseline, 24 months and 48 months for all randomised participants, and at 12, 36 months for those participants in whom a BTK mutation is detected.
- 10. Evolution of resistant sub-clones will be assessed as the proportion of BTK mutations that are identified over time. It will be assessed at baseline and following 24 and 48 months of trial treatment. If resistant subclones are present, biobank samples collected at 12 and 36 months of trial treatment, will be used to identify the onset of these subclones.

Completion date

01/09/2031

Eligibility

Key inclusion criteria

Current key inclusion criteria as of 25/09/2025:

Trial Registration Inclusion Criteria:

- 1. At least 18 years old
- 2. A diagnosis of chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) (by 2018 iwCLL criteria)
- 3. World Health Organisation (WHO) performance status (PS) of 0,1, or 2
- 4. Biochemical values must be within the following limits within 4 weeks prior to randomisation /or registration for the Clinical Need Cohort and at baseline:
- 4.1. Alanine aminotransferase (ALT) ≤ 3 x upper limit of normal (ULN) OR Aspartate aminotransferase (AST) ≤ 3 x ULN.
- 4.2. Total bilirubin ≤1.5 x ULN, unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin
- 5. Agree to follow the pregnancy prevention plan*
- 6. Able to provide informed consent
- *Participants randomised to the pause/resume arm must adhere to this whilst receiving treatment with a BTK inhibitor, but will not be required to follow contraceptive measures during the planned treatment breaks

Additional inclusion criteria for participants in the Clinical Need Cohort:

- 1. Meet all of the Registration Inclusion criteria
- 2. Currently receiving ibrutinib and nearing the end of or having completed 6 years of ibrutinib treatment on FLAIR or IcICLLe**
- 3. Have signs of progressive or returning CLL after completing 6 years of ibrutinib treatment within FLAIR or IcICLLe, but prior to entry into STATIC

Additional inclusion criteria for Front Line participants entering the randomisation trial:

- 1. Meet all of the Registration Inclusion criteria
- 2. Currently receiving front-line treatment with ibrutinib and received at least 6 years through standard care, or currently receiving front-line treatment with ibrutinib and approaching the end of 6 years of treatment in FLAIR or IcICLLe, or having already completed 6 years of ibrutinib treatment in FLAIR or IcICLLe. **
- 3. In clinical remission, all of the following:
- 3.1. No palpable lymph nodes;
- 3.2. No palpable spleen; and
- 3.3. Lymphocyte count below $5x10^9/L$ continuously for at least 12 months before randomisation
- **Patients should enter STATIC on completion of treatment in FLAIR or IcICLLe, with no break in therapy, with the exception of participants who have completed the 6 years of treatment in FLAIR or IcICLLe prior to STATIC opening

Additional inclusion criteria for Previously Treated participants entering the randomisation trial:

- 1. Meet all of the registration inclusion criteria
- 2. Currently receiving ibrutinib or acalabrutinib for at least the previous 36 months as the second or subsequent line of treatment. There is no restriction on the maximum duration of treatment prior to enrolment.
- 3. In clinical remission, fulfilling all of the following:
- 3.1. No palpable lymph nodes;
- 3.2. No palpable spleen; and
- 3.3. Lymphocyte count below 5x10^9/L at the time of assessing eligibility

Previous inclusion criteria as of 07/07/2025:

Trial Registration Inclusion Criteria:

- 1. At least 18 years old
- 2. A diagnosis of chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) (by 2018 iwCLL criteria)
- 3. World Health Organisation (WHO) performance status (PS) of 0,1 or 2
- 4. Biochemical values must be within the following limits within 4 weeks prior to randomisation /or registration for the Clinical Need Cohort and at baseline:
- 4.1. Alanine aminotransferase (ALT) ≤ 3 x upper limit of normal (ULN) OR Aspartate aminotransferase (AST) ≤ 3 x ULN.
- 4.2. Total bilirubin ≤1.5 x ULN, unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin
- 5. Agree to follow the pregnancy prevention plan*
- 6. Able to provide informed consent
- *Participants randomised to the pause/resume arm must adhere to this whilst receiving treatment with a BTK inhibitor, but will not be required to follow contraceptive measures during the planned treatment breaks

Additional inclusion criteria for participants in the Clinical Need Cohort:

- 1. Meet all of the Registration Inclusion criteria
- 2. Currently receiving ibrutinib and nearing the end or having completed 6 years of ibrutinib treatment on FLAIR or IcICLLe**
- 3. Have signs of progressive or returning CLL after completing 6 years of ibrutinib treatment within FLAIR or IcICLLe, but prior to entry into STATIC

Additional inclusion criteria for Front Line participants entering the randomisation trial:

- 1. Meet all of the Registration Inclusion criteria
- 2. Currently receiving ibrutinib in FLAIR or IcICLLe, or having completed 6 years of ibrutinib of ibrutinib in FLAIR or IcICLLe**
- 3. In clinical remission all of the following:
- 3.1. No palpable lymph nodes;
- 3.2. No palpable spleen; and
- 3.3. Lymphocyte count below $5x10^9/L$ continuously for at least 12 months before randomisation
- **Patients should enter STATIC on completion of treatment in FLAIR or IcICLLe, with no break in therapy, with the exception of participants who have completed the 6 years of treatment in FLAIR or IcICLLe prior to STATIC opening

Additional inclusion criteria for Previously Treated participants entering the randomisation trial:

- 1. Meet all of the registration inclusion criteria
- 2. Currently receiving ibrutinib or acalabrutinib for at least the previous 36 months as the second or subsequent line of treatment. There is no restriction on maximum duration of treatment prior to enrolment.
- 3. In clinical remission fulfilling all of the following:
- 3.1. No palpable lymph nodes;
- 3.2. No palpable spleen; and
- 3.3. Lymphocyte count below 5x10^9/L at the time of assessing eligibility

Previous inclusion criteria:

Trial Registration Inclusion Criteria:

- 1. At least 18 years old
- 2. A diagnosis of chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) (by 2018 iwCLL criteria)
- 3. World Health Organisation (WHO) performance status (PS) of 0,1 or 2
- 4. Biochemical values must be within the following limits within 4 weeks prior to randomisation /or registration for the Clinical Need Cohort and at baseline:
- 4.1. Alanine aminotransferase (ALT) ≤ 3 x upper limit of normal (ULN) OR Aspartate aminotransferase (AST) ≤ 3 x ULN.
- 4.2. Total bilirubin ≤1.5 x ULN, unless bilirubin rise is due to Gilbert's syndrome or of non hepatic origin
- 5. Agree to follow the pregnancy prevention plan*
- 6. Able to provide informed consent
- *Participants randomised to the pause/resume arm must adhere to this whilst receiving ibrutinib, but will not be required to follow contraceptive measures during the planned treatment breaks

Additional inclusion criteria for participants in the Clinical Need Cohort:

- 1. Meet all of the Registration Inclusion criteria
- 2. Currently receiving ibrutinib and nearing the end or having completed 6 years of ibrutinib treatment on FLAIR**
- 3. Have signs of progressive or returning CLL after completing 6 years of ibrutinib treatment within FLAIR, but prior to entry into STATIC

Additional inclusion criteria for Front Line participants entering the randomisation trial:

- 1. Meet all of the Registration Inclusion criteria
- 2. Currently receiving ibrutinib in FLAIR or having completed 6 years of ibrutinib of ibrutinib in FLAIR**

- 3. In clinical remission all of the following:
- 3.1. No palpable lymph nodes;
- 3.2. No palpable spleen; and
- 3.3. Lymphocyte count below $5x10^9/L$ continuously for at least the 12 months before randomisation
- **Patients should enter STATIC on completion of treatment in FLAIR, with no break in therapy, with the exception of participants who have completed the 6 years of treatment in FLAIR prior to STATIC opening

Additional inclusion criteria for Previously Treated participants entering the randomisation trial:

- 1. Meet all of the registration inclusion criteria
- 2. Currently receiving ibrutinib for at least the previous 36 months. There is no restriction on maximum duration of treatment prior to enrolment.
- 3. In clinical remission fulfilling all of the following:
- 3.1. No palpable lymph nodes;
- 3.2. No palpable spleen; and
- 3.3. Lymphocyte count below $5x10^9/L$ continuously for at least the 12 months before randomisation

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 years

Sex

All

Key exclusion criteria

Current exclusion criteria as of 07/07/2025:

Trial Registration Exclusion Criteria:

- 1. Pregnant females
- 2. Known intolerance or hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.
- 3. Receipt of live vaccination within 4 weeks prior to registration and for the duration of the study.
- 4. History or current evidence of Richter's transformation
- 5. Major surgery within 4 weeks prior to randomisation/or registration for the Clinical Need Cohort
- 6. Active infection
- 7. Concomitant warfarin (or equivalent vitamin K inhibitor)
- 8. Central nervous system involvement with CLL
- 9. Cardiac failure; including symptomatic cardiac failure not controlled by therapy, or unstable angina not adequately controlled by current therapy (in patients with a significant cardiac history the left ventricular function should be assessed and patients with severe impairment

should be excluded)

- 10. Respiratory impairment (e.g. bronchiectasis or severe COPD)
- 11. Other severe, concurrent diseases or mental disorders that could interfere with their ability to participate in the study
- 12. Positive serology for Hepatitis B (HB), defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), aHB DNA test will be performed and if positive, the patients will be excluded. During treatment, these participants should be monitored and managed to prevent HBV reactivation.
- 13. Positive serology for Hepatitis C (HC) defined as a positive test for HCAb, in which case reflexively perform a test for hepatitis C RNA (for example, HCV RNA PCR). If positive, the patients will be excluded.
- 14. Persisting severe pancytopenia (neutrophils $< 0.5 \times 109/L$ or platelets $< 50 \times 109/L$)unless due to direct marrow infiltration by CLL
- 15. Current treatment with prednisolone of >20mg/day
- 16. Uncontrolled Active haemolysis
- 17. History of stroke or intracranial haemorrhage within 6 months prior to enrolment.
- 18. Requirement for treatment with a strong CYP3A inhibitor or inducer
- 19. New treatment with two or more antiplatelet drugs, treatment that has been administered at a stable dose for at least 3 months prior to registration is permissible

Additional exclusion criteria for participants in the Clinical Need Cohort:

- 1. Meet none of the registration exclusion criteria
- 2. Active Disease, as per the 2018 iwCLL criteria requiring an alternative therapy.
- 3. Received treatment other than ibrutinib for CLL since completing FLAIR
- 4. Be eligible for front-line randomisation
- 5. Ibrutinib treatment break for toxicity/patient choice for more than 28 days in the last 12 months (added 07/11/2024)

Additional exclusion criteria for Front-Line participants entering the randomisation trial:

- 1. Meet any of the registration exclusion criteria
- 2. Disease progression (according to 2018 iwCLL criteria)
- 3. Ibrutinib treatment break for toxicity/patient choice for more than 28 days in the last 12 months

Additional exclusion criteria for Previously Treated participants entering the randomisation trial:

- 1. Meet any of the registration exclusion criteria
- 2. Disease progression (according to 2018 iwCLL criteria)
- 3. Ibrutinib or acalabrutinib treatment break for toxicity/patient choice for more than 28 days in the last 12 months
- 4. Any illness, disease or condition, such as active cancer or secondary primary malignancy (SPM), with a prognosis of less than 5 years
- 5. Patients with a creatinine clearance of less than 30ml/min (either measured or derived by the Cockcroft Gault formula or an alternative locally approved formula).

Previous exclusion criteria:

Trial Registration Exclusion Criteria:

- 1. Pregnant females
- 2. Known intolerance or hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.
- 3. Receipt of live vaccination within 4 weeks prior to registration and for the duration of the study.
- 4. History or current evidence of Richter's transformation

- 5. Major surgery within 4 weeks prior to randomisation/or registration for the Clinical Need Cohort
- 6. Active infection
- 7. Concomitant warfarin (or equivalent vitamin K inhibitor)
- 8. Central nervous system involvement with CLL
- 9. Cardiac failure; including symptomatic cardiac failure not controlled by therapy,or unstable angina not adequately controlled by current therapy (in patients with a significant cardiac history the left ventricular function should be assessed and patients with severe impairment should be excluded)
- 10. Respiratory impairment (e.g. bronchiectasis or severe COPD)
- 11. Other severe, concurrent diseases or mental disorders that could interfere with their ability to participate in the study
- 12. Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), aHB DNA test will be performed and if positive the patients will be excluded. During treatment, these participants should be monitored and managed to prevent HBV reactivation.
- 13. Positive serology for Hepatitis C (HC) defined as a positive test for HCAb, in which case reflexively perform a test for hepatitis C RNA (for example HCV RNA PCR). If positive the patients will be excluded.
- 14. Persisting severe pancytopenia (neutrophils $< 0.5 \times 109/L$ or platelets $< 50 \times 109/L$)unless due to direct marrow infiltration by CLL
- 15. Current treatment with prednisolone of >20mg/day
- 16. Uncontrolled Active haemolysis
- 17. History of stroke or intracranial haemorrhage within 6 months prior to enrolment.
- 18. Requirement for treatment with a strong CYP3A inhibitor or inducer
- 19. New treatment with two or more antiplatelet drugs, treatment that has been administered at a stable dose for at least 3 months prior to registration is permissible
- 20. Current treatment with any concomitant ACE inhibitors

Additional exclusion criteria for participants in the Clinical Need Cohort:

- 1. Meet none of the registration exclusion criteria
- 2. Active Disease, as per the 2018 iwCLL criteria requiring an alternative therapy.
- 3. Received treatment other than ibrutinib for CLL since completing FLAIR
- 4. Be eligible for front-line randomisation
- 5. Ibrutinib treatment break for toxicity/patient choice for more than 28 days in the last 12 months (added 07/11/2024)

Additional exclusion criteria for Front-Line participants entering the randomisation trial:

- 1. Meet none of the registration exclusion criteria
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- 1. Meet none of the registration exclusion criteria
- 2. Disease progression (according to 2018 iwCLL criteria)
- 3. Ibrutinib treatment break for toxicity/patient choice for more than 28 days in last 12 months
- 4. Any illness, disease or condition, such as active cancer or secondary primary malignancy (SPM), with a prognosis of less than 5 years
- 5. Patients with a creatinine clearance of less than 30ml/min (either measured or derived by the Cockcroft Gault formula or alternative locally approved formula).

Date of first enrolment

Date of final enrolment 01/09/2028

Locations

Countries of recruitment

United Kingdom

England

Scotland

Wales

Study participating centre St James's Hospital

Beckett Street Leeds United Kingdom LS9 7TF

Study participating centre Aberdeen Royal Infirmary

Foresterhill Road Aberdeen United Kingdom AB25 2ZN

Study participating centre Good Hope Hospital

Rectory Road Sutton Coldfield United Kingdom B75 7RR

Study participating centre Heartlands Hospital

Bordesley Green East Bordesley Green Birmingham United Kingdom B9 5ST

Study participating centre Victoria Hospital (blackpool)

Whinney Heys Road Blackpool United Kingdom FY3 8NR

Study participating centre Bradford Royal Infirmary

Duckworth Lane Bradford United Kingdom BD9 6RJ

Study participating centre Castle Hill Hospital

Entrance 3 Castle Road Cottingham United Kingdom HU16 5JQ

Study participating centre Christie Hospital

Wilmslow Road Manchester United Kingdom M20 4BX

Study participating centre Churchill Hospital

Churchill Hospital Old Road Headington Oxford United Kingdom OX3 7LE

Study participating centre Clatterbridge Hospital

Clatterbridge Hospital Clatterbridge Road Wirral United Kingdom CH63 4JY

Study participating centre Derriford Hospital

Derriford Road Plymouth United Kingdom PL6 8DH

Study participating centre Grantham and District Hospital

101 Manthorpe Road Grantham United Kingdom NG31 8DG

Study participating centre The James Cook University Hospital

Marton Road Middlesbrough United Kingdom TS4 3BW

Study participating centre Kent and Canterbury Hospitals NHS Trust

Ethelbert Road Canterbury United Kingdom CT1 3NG

Study participating centre

Kettering General Hospital

Kettering General Hospital Rothwell Road Kettering United Kingdom NN16 8UZ

Study participating centre Kings College Hospital

Mapother House De Crespigny Park Denmark Hill London United Kingdom SE5 8AB

Study participating centre Leicester Royal Infirmary

Infirmary Square Leicester United Kingdom LE1 5WW

Study participating centre Lincoln County Hospital

Greetwell Road Lincoln United Kingdom LN2 5QY

Study participating centre Milton Keynes General Hospital

Milton Keynes Hospital Standing Way Eaglestone Milton Keynes United Kingdom MK6 5LD

Study participating centre

Musgrove Park Hospital

Orthopaedic Triage Service Parkfield Drive Taunton United Kingdom TA1 5DA

Study participating centre New Cross Hospital

Wolverhampton Road Wolverhampton United Kingdom WV10 0QP

Study participating centre Northampton

Northampton General Hospital Cliftonville Northampton United Kingdom NN1 5BD

Study participating centre Nottingham University Hospitals NHS Trust - City Campus

Nottingham City Hospital Hucknall Road Nottingham United Kingdom NG5 1PB

Study participating centre Pilgrim Hospital (nuh)

Sibsey Road Boston United Kingdom PE21 9QS

Study participating centre

Poole

Poole Hospital Longfleet Road Poole United Kingdom BH15 2JB

Study participating centre Princess Royal University Hospital

Farnborough Common Orpington United Kingdom BR6 8ND

Study participating centre Queen Alexandras Hospital

Southwick Hill Road Cosham Portsmouth United Kingdom PO6 3LY

Study participating centre Gateshead Hospitals NHS Trust

Queen Elizabeth Hospital Sherriff Hill Gateshead United Kingdom NE9 6SX

Study participating centre

University Hospitals Birmingham NHS Foundation Trust

Queen Elizabeth Hospital Mindelsohn Way Edgbaston Birmingham United Kingdom B15 2GW

Study participating centre Queens Hospital

Rom Valley Way

Romford United Kingdom RM7 0AG

Study participating centre Rotherham District General Hospital

Moorgate Road Rotherham United Kingdom S60 2UD

Study participating centre Royal Bournemouth General Hospital

Castle Lane East Bournemouth United Kingdom BH7 7DW

Study participating centre Royal Cornwall Hospitals NHS Trust

Royal Cornwall Hospital Treliske Truro United Kingdom TR1 3LJ

Study participating centre

Royal Devon University Healthcare NHS Foundation Trust

Royal Devon University NHS Ft Barrack Road Exeter United Kingdom EX2 5DW

Study participating centre Royal Hampshire County Hospital (rhch)

Romsey Road Winchester United Kingdom SO22 5DG

Study participating centre Russells Hall Hospital

Pensnett Road Dudley United Kingdom DY1 2HQ

Study participating centre Salisbury District Hospital

Salisbury District Hospital Odstock Road Salisbury United Kingdom SP2 8BJ

Study participating centre Southmead Hospital

Southmead Road Westbury-on-trym Bristol United Kingdom BS10 5NB

Study participating centre St. Bartholomews Hospital

West Smithfield London United Kingdom EC1A 7BE

Study participating centre St Georges

St. Georges Hospital 117 Suttons Lane Hornchurch United Kingdom RM12 6RS

Study participating centre

Stoke Mandeville Hospital

Mandeville Road Aylesbury United Kingdom HP21 8AL

Study participating centre Torbay and South Devon NHS Foundation Trust

Torbay Hospital Newton Road Torquay United Kingdom TQ2 7AA

Study participating centre University College London Hospitals NHS Foundation Trust

250 Euston Road London United Kingdom NW1 2PG

Study participating centre University Hospital Crosshouse

Kilmarnock Road Kilmarnock United Kingdom KA2 0BE

Study participating centre Monklands District General Hospital

Monkscourt Avenue Airdrie United Kingdom ML6 0JS

Study participating centre University Hospital of Wales

Heath Park Cardiff United Kingdom CF14 4XW

Study participating centre West Middlesex University Hospital

Twickenham Road Isleworth United Kingdom TW7 6AF

Study participating centre The Worcestershire Royal Hospital

Newtown Road Worcester United Kingdom WR5 1ZL

Study participating centre York Hospital

Wigginton Road York United Kingdom YO31 8HE

Study participating centre The Royal Marsden Hospital (surrey)

Downs Road Sutton United Kingdom SM2 5PT

Study participating centre Royal Shrewsbury Hospital

Mytton Oak Road Shrewsbury United Kingdom SY3 8XQ

Study participating centre Ysbyty Gwynedd Hospital (yg NHS Trust)

Ysbyty Gwynedd

Penrhosgarnedd Bangor United Kingdom LL57 2PW

Study participating centre Wrexham Maelor Hospital

Croesnewydd Road Wrexham Technology Park Wrexham United Kingdom LL13 7TD

Study participating centre Ipswich Hospital

Heath Road Ipswich United Kingdom IP4 5PD

Sponsor information

Organisation

University of Leeds

ROR

https://ror.org/024mrxd33

Funder(s)

Funder type

Government

Funder Name

Health Technology Assessment Programme

Alternative Name(s)

NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

Funder Name

Janssen-Cilag Limited

Funder Name

National Institute for Health Research

Alternative Name(s)

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes